Acta Medica Mediterranea, 2010, 26: 29

TWO CASES OF NON-ALCOHOLIC WERNICKE ENCEPHALOPATHY SUCCESSFULLY TREATED BY THIAMINE REPLACEMENT: DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

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[Due casi di encefalopatia di Wernicke non-alcolica trattati con successo con somministrazione di tiamina: considerazioni diagnostiche e terapeutiche]

SUMMARY

Wernicke's encephalopathy (WE) is an acute neurological disorder, due to a lack of thiamin (vitamin B1) which is observed mainly in alcoholic patients. Unfortunately, the syndrome is underestimated in clinical practice and most often recognized only on autopsy, especially among non-alcoholics. The common clinical picture include mental status changes, ocular dysfunction, and gait ataxia. Treatment consists of timely thiamine replacement through intravenous infusion.

We describe the case of two patients who developed a non-alcoholic WE post-surgical, regressed completely after intravenous infusion of thiamine. These cases suggest interesting diagnostic and therapeutic implications.

Key words: Wernicke's encephalopathy, thiamine, total parenteral nutrition

RIASSUNTO

L'encefalopatia di Wernicke (EW) è un disordine neurologico acuto dovuto ad un deficit di tiamina (vitamina B1) che interessa prevalentemente i soggetti alcolisti. Purtroppo, tuttavia, la sindrome è sottodiagnosticata nella pratica clinica e più spesso riconosciuta solo dopo autopsia, soprattutto tra i non-alcolisti. Il quadro clinico comune comprende alterazioni dello stato mentale, disfunzioni oculari ed atassia. Il trattamento consiste nella tempestiva somministrazione di tiamina tramite infusione endovenosa.

Noi descrivono il caso di due pazienti che sviluppavano una EW non-alcolica post-chirurgica, che regrediva completamente dopo infusione endovenosa di tiamina. Tali casi suggeriscono interessanti implicazioni diagnostiche e terapeutiche.

***Parole chiave**: Encefalopatia di Wernicke, tiamina, nutrizione parenterale totale*

Introduction

Wernicke's encephalopathy (WE) is an acute neurological disorder resulting from thiamin (B1 vitamin) deficiency, which is observed mainly in alcoholic patients[1]. However, in recent years, several cases of WE were reported to coincide with other clinical settings such as hyperemesis gravidarum, prolonged fasting, chemotherapy treatments, gastrectomy surgery, tumors or other chronic systemic disease[2]. Recently, some cases of WE were reported in patients receiving total parenteral nutrition (TPN)[3].

The diagnosis of WE is primarily based on clinical data and medical history. This disorder should be considered in all subjects that show an acute onset of disturbance of consciousness, possibly associated with ataxia and paralysis of gaze. The presumptive diagnosis of WE can be confirmed by

the neuroimaging studies. MRI is currently considered the most value method to confirm the diagnosis of WE. Characteristic findings include bilateral and symmetrical areas of increased signal intensity on T2-weighted and FLAIR images, in the dorsomedial portion of the thalami, in the periaqueductal region and in the tectum of the midbrain[7-9]. MRI sequences DWI showed symmetrical pathologic thalamic and midbrain signal hyperintensities more distinctly than did conventional T2-weighted or FLAIR sequences[5,6].

We describe two cases of non-alcoholic Wernicke's encephalopathy that developed during total parenteral nutrition, due to lack of vitamin supplementation. This disorder was treated successfully by thiamine administration.

Case reports

Case 1: A 76-years-old man, in February 2008, was admitted in a department of emergency surgery for a history of 2 weeks of rectal bleeding and colic pain in the lower abdominal quadrants. The patient

was suffering from arterial hypertension treated by pharmacological agents, with good control of blood pressure. He was suffering also from diabetes mellitus type II complicated by severe lower limbs ischemia for which he had undergone surgery for amputation of the right leg. It was no reported history of alcoholism, substance abuse or poor nutrition for strict diet.

A physical examination, including neurological status, performed at the admission was normal with the exception of symptoms that had motivated the hospitalization. Laboratory investigations demonstrated only a modest sideropenic anemia.

During the hospitalization, a colorectal adenocarcinoma was diagnosed and, in March 2008, the patient underwent surgical anterior rectal resection with colorectal proctoanastomosi. After the surgery, he began a total parenteral feeding regimen that was prolonged because of a surgical complication (rectal fistula).

About 20 days later, the patient acutely presented the onset of symptoms characterized by drowsiness, confusion, spatial-temporal disorientation, diplopia and ataxia. A neurological examination demonstrated normal size of pupils that were reacted to the light, bidirectional horizontal nystagmus and ataxia. The results of electroencephalography (EEG) showed non-specific slowing of the dominant rhytm. A brain computed tomography (CT) showed no significant abnormality, except for the presence of a modest cortical-subcortical atrophy. Six days after onset of clinical symptoms, also a brain magnetic resonance imaging (MRI) was performed. T2-weighted and fluid-attenuated inversion recovery (FLAIR) images revealed bilateral and symmetrical hyperintense lesions within the dorsomedial thalami, periaqueductal white matter, and in the tectum of the midbrain (Fig.1a). In addition to conventional MRI sequences, diffusion-weighted imaging (DWI) were performed that confirmed more clearly the symmetrical pahologics thalamic and midbrain signals hyperintensities. Cerebrospinal fluid studies were unremarkable, and viral and bacterial cultures were negative. Routine blood investigations were unchanged from those reported at the admission.

Therefore, Wernicke's encephalopathy was diagnosed and the patient was immediately treated with additional daily thiamine administration (300 mg per day i.v. for 7 consecutive days). Repeated neurological evaluations revealed a slight but progressive improvement in the clinical picture, with complete resolution of symptoms after two months. Remission of the clinical picture was supported also by neuroradiologic investigations that showed a complete regression of the changes described above.

Case 2: A 47-years-old woman, in November 2007, was conducted in the emergency area for the occurrence of recurrent episodes of biliary colic for which the patient underwent surgery to videolaparotomy-colecistectomy. The medical history showed the presence of an anxiety-depression syndrome, treated with antipsychotics and an history of gastric ulcer treated with gastrectomy surgery and esophagus-digiunostomy. Five days later, the patient was hospitalized for sudden onset of epigastric acute pain, associated with marked weakness and profuse sweating. During hospitalization, a severe acute peritonitis secondary to perforation of the gallbladder, complicated by duodenal micro-perforations was diagnosed. Therefore, the patient underwent surgical treatment. During the postoperative she began a total parenteral feeding regimen that was prolonged because of the onset of acute pancreatitis.

Approximately two months after the surgery, the patient presented an acute onset of symptoms including gait instability, double vision and psychotic symptoms as depression and paranoid delusions. A neurological examination revealed the presence of diplopia, vertical spontaneous nystagmus, tremor and ataxia with postural instability. Moreover, psychomotor agitation, drowsiness, confusion and disorientation with confabulation, and impaired verbal and nonverbal memory were also evident. Results of electroencephalography (EEG) showed non-specific slowing of the dominant rhytm. Cerebrospinal fluid was normal and showed only a slight increase of protein, while the culture analysis was negative. A brain MRI studies typically demonstrated, in T2-weighted and FLAIR sequences, increased bilateral and symmetrical signal localized in the paraventricular regions of the thalamus, mammillary bodies, periaqueductal region (Fig.1b). Therefore, the patient was promptly treated with daily administration of thiamine (300 mg per day i.v. for two months). Subsequent neurological evaluations revealed a slight but progressive improvement in the clinical setting. Only four days after the treatment, she was alert and showed an improvement of memory and orientation, even if she was not yet able to maintain balance or walk without assistance. Four months after treatment, the patient showed complete resolution of neurological symptoms. Consistent with this clinical data, also neuroimaging showed complete resolution of changes.

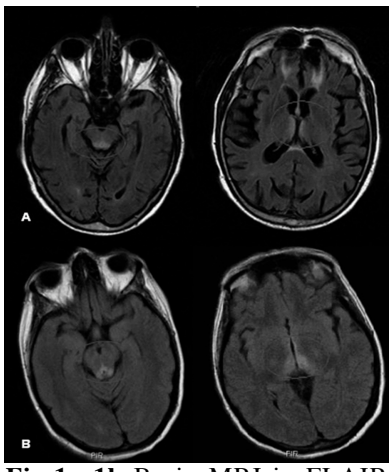

Fig.1a-1b: Brain MRI in FLAIR sequences, in the first (Fig.1a) and second patient (Fig.1b), showing the characteristics hyperintensities of the WE that are localized, with symmetrical distribution, in the tectum of the midbrain, periaqueductal region and dorsomedial thalami.

Discussion

Wernicke's encephalopathy (WE) is an acute neurological disorder, clinically characterized by oculomotor disturbances, ataxia and mental-status changes. These symptoms may occur singly, but more often are present in various combinations[4].

The most common onset of symptoms is the altered state of consciousness that occurs more frequently as a global confusional state. The patient appears apathetic, inattentive and indifferent to environmental stimuli. Spontaneous verbal communication is minimal. The memory and learning abilities are impaired. The oculomotor abnormalities are represented by nystagmus, paralysis of the abducens and of the conjugate eye movements. The third symptom of the disease is ataxia, which manifests primarily as gait instability; in fact disorders of the coordination of limbs are rare. Autonomic dysfunction and peripheral neuropathy are also been observed[1].

Although alcoholism is responsible for most cases of WE, in the past two decades it was more frequently diagnosed in non-alcoholics patients with a variety of diseases responsible for a state of severe nutritional deficiency[2]. In addition, recent evidence shows that many patients undergoing a regime of total parenteral nutrition (NPT), due to the absence of an adequate supplement of thiamine, have developed such syndrome in a few weeks[3].

Thiamine deficiency (TD) is the underlying cause of WE[10]. Although the neurologic dysfunction and brain damage that results from TD has been well-described, the precise mechanisms that lead to the selective histological lesions characteristic of this disorder remain unknow. Over the course of many years, various processes have been proposed as responsible of the focal neuronal cell death in this pathological condition[13].

Thiamine is an important co-factor of several enzymes, including the transketolase, pyruvate dehydrogenase el'α-ketoglutarate dehydrogenase. It is essential in maintaining osmotic gradients across cell membranes and plays an important role as a coenzyme in both the Krebs and the pentose-phosphate cycle[4]. In its biologically active form, thiamine pyrophosphate (TPP), is an essential coenzyme in several biochemical pathways in the brain[11,12], such as intermediate carbohydrate metabolism (for energy production by ATP synthesis), lipid metabolism (for production and maintenance of myelin sheath), and production of aminoacids and glucose-derived neurotransmitters (glutamic acid; GABA)[10-13]. Therefore, a deficiency of thiamine in the brain causes a widespread reduction in the use of glucose, causing mitochondrial damage. Due to the deficient activity of α-ketoglutarate dehydrogenase, an accumulation of glutamate occurs that, combined with the energy gap, helps to determine an excito-toxic cell damage[12].

We describe two cases of non-alcoholic Wernicke's encephalopathy that developed during total parenteral nutrition, due to lack of vitamin supplementation.

Diagnosis of WE was initially made clinically on the basis of the presence of the classic triad including ataxia, ocular motility disorders and confusion and successively confirmed by neuroimaging studies. The brain MRI (T2-weighted, FLAIR, DWI) typically showed the characteristics hyperintensities that were symmetrically distributed and localized in the dorsomedial thalami, periaqueductal white matter, and in the tectum of the midbrain[5-9]. The good response to treatment with thiamine finally confirmed the diagnosis. It is interesting note that the complete remission of the clinical picture, obtained in a few months, was also in agreement with the neuroradiological data that revealed the complete regression of the alterations previously described in the brain MRI.

Therefore, these cases suggest the need to consider the diagnosis of EW in all subjects in NPT that

show an acute onset of mental-status change possibly associated with ataxia and oculomotor abnormalities. Although WE is a potentially reversible disorder, it remains a pathologic condition often ignored and untreated, especially in non-alcoholic patients, so that it progress towards a fatal evolution. Indeed WE constitute a medical emergency that, if early recognized and promptly treated, may regress completely in a relatively short period of time. Therefore, in patients with suspected WE, intravenously thiamine administration should be initiated immediately. The prompt parenteral administration of high-dose of thiamine can arrest disease progression and determine a rapid and complete remission of the neurological deficits within some weeks or few months. The remission of clinical picture can be monitored using neuroradiologic investigations, that may show the regression of those lesions that have not yet reached the level of permanent structural alteration.

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